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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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KATTEN MUCHIN ZAVIS ROSENMAN
525 WEST MONROE STREET
CHICAGO, IL 60661-3693

EXAMINER	
WOITACH, JOSEPH T	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 01/25/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/534,487	REID ET AL.	
	Examiner	Art Unit	
	Joseph T. Woitach	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 September 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *21,23,25,27,29-36 and 39-43* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *21, 23, 25, 27, 29-36, 39-43* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

This application is a continuation of 09/115,920, now US Patent 6,146,899, which is a continuation of 08/751,546, now US Patent 5,789,246, which is a divisional of application 8/165,696, now US Patent 5,576,207, which is a continuation 7/741,128, now abandoned.

Applicants' amendment filed November 11, 2004, has been received and entered. Claims 1-20, 22, 24, 26, 28, 37 and 38 have been cancelled. Claims 21, 23, 25, 27, 29-36, 39-43 are pending.

For clarity of the record, it is noted that claims 21, 40 and 41 were amended in the non-compliant amendment filed on August 2, 2004. In the instant listing of claims the amendments to these claims have been presented without editor marks and the claims have been indicated to be 'previously presented'. This is not correct because the amendment filed August 2, 2004 was not entered. However, to expedite prosecution the instant claims listing as provided in the instant amendment will be considered.

Further, it is noted that no new or alternative arguments have been filed in the last two attempts to correct the listing of the claims. The arguments filed March 25, 2004 will be considered in the instant action.

Claims 21, 23, 25, 27, 29-36, 39-43 are pending and currently under examination.

Claim Objections

Claims 21 is objected to because of the following informalities: the final phrase 'and is administered to the subject' is now redundant in light of the new claim amendments. Previously, the claim recited that the cell be used was removed from the subject, now no specific recitation exists. While it is implicit that the cell is removed to genetically engineer it *ex vivo*, the prior portion of the claim clearly indicates the method step that the cell is administered.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 41 and 42 stand rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicants note the amendment to the claims, in particular the deletion of 'histocompatible normal' and 'normal' from the claims and argue that the rejection has been obviated. See Applicants' amendment, pages 8-9, Section A. Applicants comments and arguments have been fully considered, and not found persuasive.

As noted previously, the specification provides no literal support for the term 'histocompatible'. More importantly, the specification teaches the contrary in that a wide variety

of sources can be used, not requiring a 'histocompatible' match because 'immature cells may also be less likely to stimulate immune rejection' (see page 15, lines 6-10). The specification teaches that a clear advantage to the disclosed invention is that the usual requirement of matching the histological markers of various subjects is not needed or required if the disclosed precursor cell is used.

Claims 21, 23, 25, 27, 29-36, 39-43 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention

Specifically, claims 21 and 40 have been amended to indicate that the hepatocyte precursor cell used in the claimed methods and product "is obtained by expanding isolated immature cells obtained from said subject to enrich for hepatocyte precursor cells". Applicants note that support for the amendment is on page 2 lines 1-5 and 8-14 (see remarks section, top of page 6). Review of these sections of the specification and review of the complete specification while generally supporting isolation of hepatocyte precursor cells does not support the specific teaching or required methodology to practice the method as claimed. The parts of the specification noted by applicants indicate the isolation of "hepatocyte precursors" from the liver or other tissues that contain hepatocyte precursor cells, but nowhere in the specification is there the detail for the specific methodology of expanding immature cells from any tissue to provide hepatocyte precursor cells as broadly claimed. 37 CFR 1.118 (a) states that "No amendment

shall introduce new matter into the disclosure of an application after the filing date of the application".

To the extent that the claimed compositions and/or methods are not described in the instant disclosure, claims 21, 23, 25, 27, 29-36, 39-43 are also rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention, since a disclosure cannot teach one to make or use something that has not been described and will be discussed below in greater detail.

MPEP 2163.06 notes "If new matter is added to the claims, the examiner should reject the claims under 35 U.S.C. 112, first paragraph - written description requirement. In re Rasmussen, 650 F.2d 1212, 211 USPQ 323 (CCPA 1981)." MPEP 2163.02 teaches that "Whenever the issue arises, the fundamental factual inquiry is whether a claim defines an invention that is clearly conveyed to those skilled in the art at the the time the application was filed...If a claim is amended to include subject matter, limitations, or terminology not present in the application as filed, involving a departure from, addition to, or deletion from the disclosure of the application as filed, the examiner should conclude that the claimed subject matter is not described in that application. MPEP 2163.06 further notes "When an amendment is filed in reply to an objection or rejection based on 35 U.S.C. 112, first paragraph, a study of the entire application is often necessary to determine whether or not "new matter" is involved. Applicant should therefore specifically point out the support for any amendments made to the disclosure".

Claims 21, 23, 25, 27, 29-36, 39-43 stand rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention

Applicants summarize the rejection set forth in the previous office action, and note the amendment to claims 21 and 40 to more specifically point out and distinctly claim what Applicnants regard as their invention (Applicants' amendment Section B, pages 9-10). Noting the claims that have been allowed, Applicants argue that the present breadth of the claims are consistent with that of 6,146,889 and 5,789,246 (Applicants' amendment Section B, pages 10-11). In addition, Applicants argue that Examiners recognition that a "a necessary and defining characteristic of a hepatocyte precursor cell" is the ability of the precursor cell to differentiate into a hepatocyte, and that without evidence to the contrary the literal support in the present specification for the properties of the claimed cells should not be doubted and is improper (Applicants' amendment Section B, page 12). See Applicants' amendment Section B, pages 9-12. Applicants' arguments have been fully considered, but not found persuasive.

First, with respect to the claim amendments, similar to that which was indicated in the previous office action, Examiner would agree that amendments to the claims to be drawn to use of cells that can be obtained and expanded from the subject which is to be treated addresses the basis of the rejection which focuses on the rejection of engrafted cells in a subject due to the immune reaction generated to cells comprising foreign antigens, as with the administration of autologous cells. However, the two main points of enablement remain at issue; first, the ability of the disclosed composition of precursor cells to serve as hepatocyte precursor cells for

treatment when placed into a subject, and second the lack of necessary guidance and skill in the art to provide treatment of a specific liver dysfunction by genetically engineering a hepatocyte precursor cell. Neither of the two issues above dispute the claims that have been allowed in patents '246 and '546, or the portion of the instant claims that are encompass these embodiments. More specifically, the instant rejection revolves around issues of enablement that focus on the use of the products in the methods of treatment, not the products or the methods used to make the claimed products. With respect to claim 40, the single product claim, it is included in the basis of the rejection because of its implicit intended use, and for the fact that the specification only provides conditions and methods for isolating the precursor cells in the context of a composition of cells (see for example US Paten 6,146,889) and does not provide any guidance to isolate a population of hepatocyte precursor cells as a starting material. The specification provides evidence that hepatocyte precursor cells exist in a composition of cells isolated from total liver, however the specification fails to provide the necessary guidance or details on how one would isolate the materials, i.e. hepatocyte precursor cells, to practice the instantly claimed method or make the drug delivery system. The specification discusses that such cells could be isolated from the composition by methods known in the art, such as through the use of antibodies, however there is no detailed discussion of what these antibodies are. While the specification does not have to teach what is well known in the art such as methods of isolation, it is required to teach that which is not well known. Clearly, further characterization of the precursor cell would be required to practice any method of isolation known at the time of filing. Simply reciting that a cell exists and functional properties of a cell does not provide an enabling disclosure for isolating the cell. This is particularly important in this case because the

presumed novelty of the allowed precursor cells. In addition, while the cell has observable functional properties *in vitro*, this does not provide any substantive teaching nor examples demonstrating that hepatocyte precursor cells isolated in this manner will maintain a precursor like state or will differentiate into mature hepatocytes *in vitro* or *in vivo* if engrafted back into a subject. Again, there is no evidence that the claimed cells isolated by the methods disclosed in the present specification have the ability to differentiate into hepatocytes. As indicated previously, the present specification provides no such evidence. Moreover, the Examiner has cited Debeva *et al.* as supporting evidence that even if one were to concede that the cells would or could differentiate in vivo, the specification fails to provide the enabling disclosure for the proper process required for the delivery of a hepatocyte precursor cell to a subject. The specification presents only a prophetic description for the potential use of the hepatocyte precursor cells in obtaining a genetically engineered hepatocyte precursor but does not demonstrate that one can isolate, culture or place these cells back into an *in vivo* context in a subject by any means as required by the instant claims.

With regard to isolating cells from any of the in vitor cultures, the specification provides no specific epitopes for the contemplated precursor cells, potentially supporting only the absence of specific genes which are expressed in more differentiated cells. Again the term "hepatocyte precursors" recited in the claims is not specifically defined in the specification, however is indicated to be used to describe a cell population that "has been culture under conditions which result in expansion of the immature cells" (page 1, lines 16-17). This term as broadly described and supported by the instant specification encompasses immature cells from any source obtained by any means. This interpretation of the breadth of the claim is more specifically supported by

the specification stating that the precursor cells can be obtained sources other than the liver, "sources, such as, but not limited to, the pancreas, gut, lung, and bone marrow" (page 1, lines 22-24 and allowed claims). Again Examiner acknowledges 'that the capability of a hepatocyte precursor cells to differentiate into a hepatocyte "is a necessary and defining characteristic of a hepatocyte precursor cell" (Applicants' amendment middleof page 11; Examiners action paper number 7, page 13), however the specific basis of the rejection is that the specification fails to provide the necessary guidance or details of the identifying features of these cells which are indicative or predict this characteristic. Thus, the specification fails to provide the necessary guidance to obtain such a population from the breadth of sources and resulting compositions encompassed by the teaching of the specification.

While the specification provides general guidance for mincing and dissociating cells of a tissue, and reduces to practice the culturing of a composition of cells isolated from liver. At the time of filing and today the artisan believed that the liver may contain stem cells, therefore it would not be contested that the facile methodology reduced to practice resulted in a composition of cells which comprised hepatocyte precursor cells, however while stem cells may exist in other tissues there is no evidence of record that hepatocyte precursor cell exists in other tissues. Further, while other culturing conditions are generally contemplated, the specification fails to provide the means to these specific conditions. Moreover, without any specific or defining feature of a hepatic precursor cell maintained in the disclosed composition of cultured cells, the skilled artisan would not even be able to optimize conditions if such a precursor cell existed in tissues other than the liver. Examiner acknowledges the subject matter that has been set forth in US patents to which the instant application claims priority, however the subject matter

determined to be enabled and patentable is not equal in scope with that instantly claimed. Importantly in this case, the instant claims do not use or require the composition of cells claimed in US patent 5,789,246. Further, it is noted that patentability of a product only requires one enabled use and does not by itself enable all potential uses of said product, and therefore would not provide a presumptive rebuttal of a *prima facie* case of lack of enablement for any method using said product. In this case the claims to the allowed product are not the same as the product used in the instantly claimed methods, nor does the existence of such a cell in a composition provide for any prophetic use of said cell.

Finally, the ability to make a genetically altered cell by transforming a cell with a gene of interest in culture is not at issue. Examiner acknowledges that specific methodology for models of *ex vivo* gene therapy are currently being developed in the art. With respect to the references provided by Applicants, the only reference relevant to the instantly claimed method is that of Dabeva *et al.* because the remaining references deal with hematopoietic stem cells not hepatocyte precursor cells. Hematopoietic stem cells are present in the circulation or bone marrow and can only be used in particular therapies associated with lineages of these cell types. None of the specific methodology or genes of interest for this technology would be applicable to the instantly claimed methods. With respect to the teachings of Debeva *et al.* initially it is noted that the FLEC used by Debeva *et al.* are not the same as used in the instantly claimed methods, nor are they obtained by the methods disclosed in the instant specification therefore does not by itself provide evidence that the cells disclosed in the instant specification and used in the instantly claimed method would differentiate into hepatocytes when placed into the liver of a subject. Even if one to concede that the hepatocyte precursor cells present in the composition of

cells enabled by the instant application would differentiate *in vivo*, Debeva *et al.* teach that the method needed to successfully engraft cells into the liver require partial hepatectomy which is not taught in the instant specification. The specification recites the potential usefulness of genetically engineered hepatocyte precursor cells for treatment of liver dysfunction, and provides a curt description of methodology for inserting a gene of interest and administering said cell for treatment, wherein treatment is affected by expression of a missing or mutated endogenous gene, expression of antisense polynucleotides to suppress expression of an undesired gene (pages 12-14; starting at line 4). With respect to instant application, there is no specific guidance nor examples on how one would treat any liver dysfunction. For example, the specification provides a general description of how one could treat hypercholesteremia by expressing the LDL gene in said cells, however there is no specific guidance on the type of promoter to use, the level of LDL expression one would need to treat a subject or if these cells would proliferate in a subject, how many cells to transplant. Another example describes the treatment of hepatitis infection by expression of anti-sense polynucleotides, however there is no guidance to what oligonucleotides would generate any treatment, what levels of expression one need to inhibit any function of any aspect of viral pathology, or how expression of a polynucleotide in a transplanted cell would affect any form of treatment in other surrounding cells. There is no guidance in the specification nor the art of record on how one would target and insert a gene of interest into said cells to create a genetically modified cell. The present specification has not provided any guidance to serve as a nexus between the art recognized obstacles of gene therapy protocols and treatment of any liver dysfunction.

Besides the general expectation that it will require years of further research to develop effective gene therapy (Anderson, page 30), it would require extensive research to understand the fundamental biology of the system. Applicants have described a method to isolate a composition of cells comprising hepatocyte precursor cells from the liver, however essentially all of the work required to genetically engineer the cells with the appropriate gene for a particular liver dysfunction, use of the cells for treatment *in vivo*, and the proper route of administration to affect treatment has been left for others.

35 U.S.C. § 112 requires that the scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art. *In re Fisher*, 166 USPQ 18, 24 (CCPA 1970), and that the specification must teach those of skill in the art how to make and how to use the invention as broadly claimed. *In re Goodman*, 29 USPQ2d at 2013 (Fed. Cir. 1994), citing *In re Vaeck*, 20 USPQ2d at 1445 (Fed. Cir. 1991). In this case determining whether the specification is enabling, one considers whether the claimed invention provides sufficient guidance to practice the claimed invention, if not, whether an artisan would require undue experimentation to make and use the claimed invention and whether working examples have been provided. When determining whether a specification meets the enablement requirements, some of the factors that need to be analyzed are: the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples, and whether the quantity of any necessary experimentation to make or use the invention based on the content of the disclosure is "undue" (MPEP 2164.01(a)). The instant specification is not enabling for the claimed invention because the specification does not provide

sufficient guidance, evidence or exemplification so that an artisan of skill would have been able to make and use the invention as claimed without undue experimentation. The ability to isolate a cell can be straightforward if such a cell is adequately described, however there is no specific structural description of a hepatocyte precursor cell in the present specification. Moreover, the present specification simply proposes the use of said cells in methods of treatment without providing any specific guidance in a highly unpredictable and yet unsuccessful field of gene therapy. In this case, in view of the of the lack of guidance, working examples, breadth of the claims, skill in the art and state of the art at the time of the claimed invention, it would require undue experimentation by one of skill to practice the invention as claimed.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 40 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claim has been amended to be a product by process requiring that the cell in the system be isolated from "from said subject", however this appears to be directed to an intended use and not a structural limitation because the cell could be used in any subject as taught in the instant specification. The amendment is a relevant use of the claimed product which renders it indefinite because it depends on how it is used.

Conclusion

No claim is allowed. The claims are free of the art of record because at the time of filing methods of isolating hepatocyte precursor cells and use of said cells in methods of treatment while generally contemplated were not enabled because details for obtaining and expanding such hepatocyte precursor cells were not known. Similarly, with respect to using genetically engineered cells to treat a dysfunction, while it was generally proposed at the time of filing that one could treat a genetic disease by providing a functional transgene to offset the problems of an inherited disease, even today this facile approach has not been attained.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joseph Woitach whose telephone number is (571) 272-0739.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla, can be reached at (571) 272-0735.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group analyst Dianiece Jacobs whose telephone number is (571) 272-0532.

Joseph T. Woitach

Joe Woitach
AU1632